Human Health Models

in vitvo Estrogen Receptor binding

Laboratory of Mathematical Chemistry, Bulgaria

The role of metabolism in predicting estrogen receptor binding affinities of xenobiotics

OUTLOOK

- Experimental test for estrogen receptor (ER) binding
- The role of xenobiotic metabolism in the ER binding process
- OASIS TIMES Model for prediction of ER binding affinity accounting for metabolic activation of xenobiotic chemicals

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Experimental test for estrogen receptor (ER) binding

- The standard test assess the binding affinity of the parent chemicals only.
- The test is not accounting for the metabolic activation of the studied chemicals.

However, there are evidences that chemicals that are non ER binders as parent structures can be metabolically transformed and some of the generated metabolites could be able to bind to the ER*.

*****M. Shelby, R. Newbold, D. Tully, K. Chae, and V. Davis, Assessing environmental chemicals for estrogenicity using a combination of in vitro and in vivo assays, Environ. Health Perspect. 104 (1996), pp. 1296–1300.

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The role of xenobiotic metabolism in the ER binding process

- The xenobiotics are taken up by the liver where they will be biotransformed further in to different metabolites which may be able to bind the ER.

- The major biotransformations involved in generation of metabolites with ER binding potential are oxidative reactions generated by cytochrome P450 (CYP) 2B1, 1A1 and 3A1.

    - *Aromatic ring hydroxylation*
    - *Aromatic O-dealkylation*

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OASIS TIMES ER binding model*

Combining in same modeling platform:

- **Toxicodynamic model –**mechanistically sound QSAR model for Estrogen Receptor binding affinity
- **Toxicokinetic model – e.g.,** simulating metabolism

* O. Mekenyan and R. Serafimova. Mechanism-Based Modeling of Estrogen Receptor Binding Affinity A COREPA Implementation. CRC Press, (2009), pp. 259-293, ISBN 978-1-4200-7636-3

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Example of a chemicals which act as ER binders after metabolic activation

Methoxychlor (CAS 72-43-5)

Methoxybiphenyl (CAS 613-37-6)

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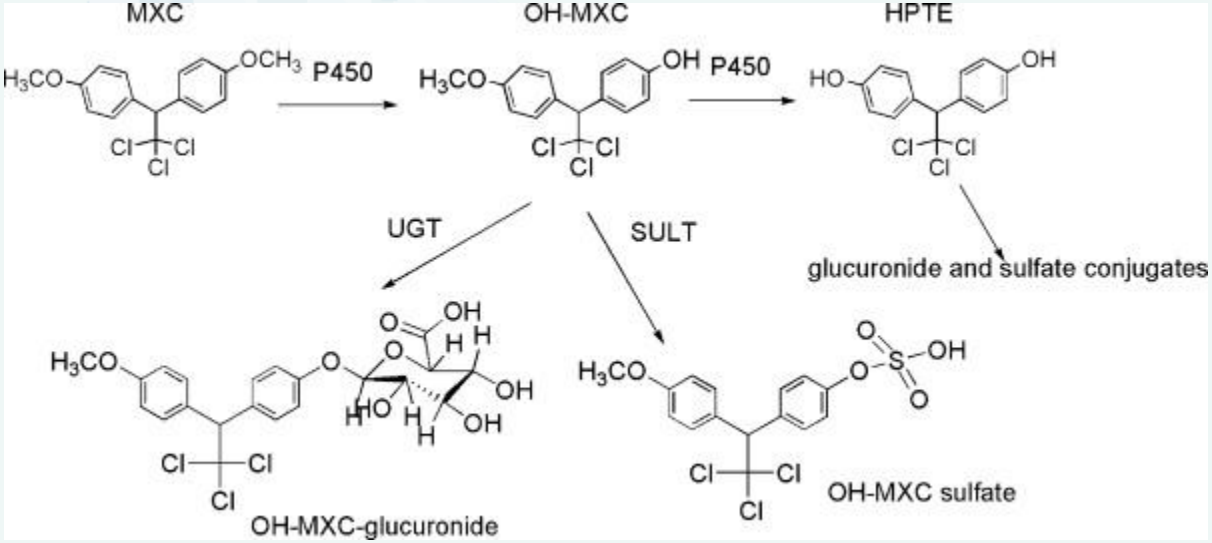
Methoxychlor (CAS 72-43-5).
The chemical has very low estrogenic activity however its metabolite 2,2-bis(p-hydroxyphenyl)-1,1,1-trichloroethane (HPTE) is stronger estrogen binder [1].

Observed metabolism of Methoxychlor (MXC) [2].



1. Gaido, K.W., Leonard, L.S., Maness, S.C., Hall, J.M., McDonnell, D.P., Saville, B & Safe, S. (1999). Differential interaction of the methoxychlor metabolite 2,2-Bis-(phydroxyphenyl)- 1,1,1-trichloroethane with estrogen receptors α and β. Endocrinology 140, 5746-5753.
2. Margaret O. James, Leah D. Stuchal, Beatrice A. Nyagode. Atox. , 86(2), 2008pp.227–238

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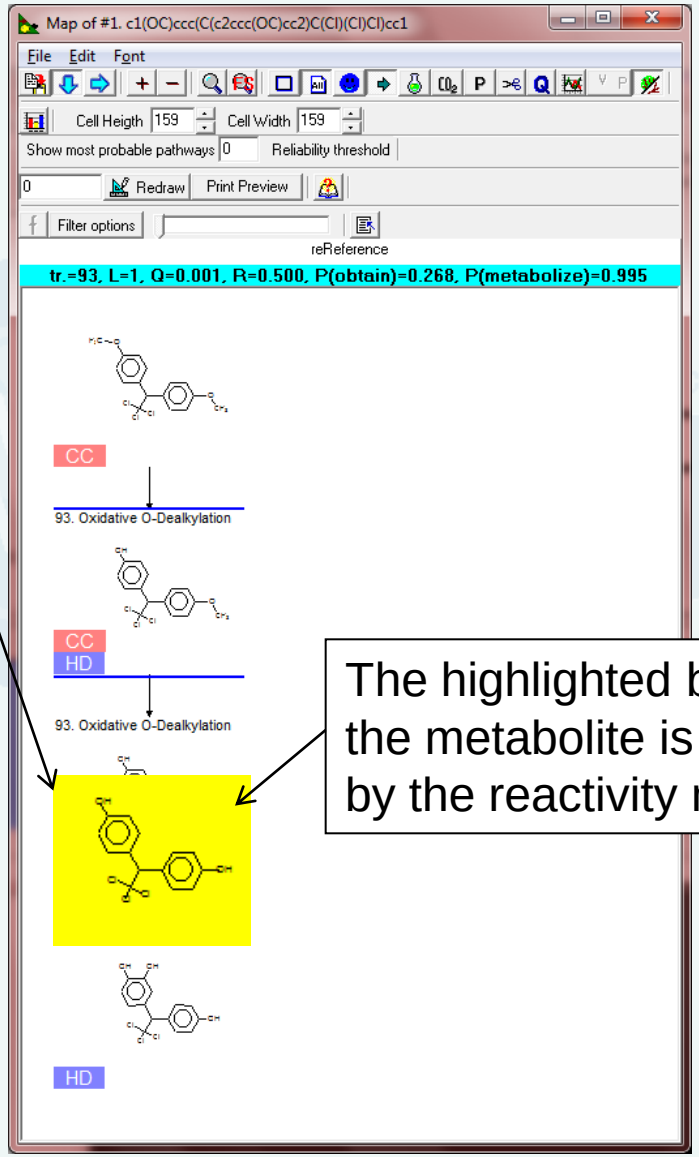
Simulated metabolic tree of Methoxychlor in TIMES platform



Applied biotransformation *Aromatic O-dealkylation*

The highlighted background means that the metabolite is predicted as ER binder by the reactivity model

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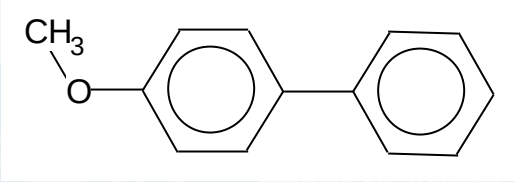
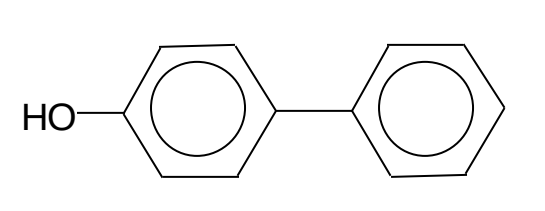
Methoxybiphenyl (CAS 613-37-6).
The chemical is not ER binder as parent structure [1].



Its metabolite *4-hydrohybiphenyl* (CAS 92-69-3), which is observed *in vitro* [2] is estrogen binder [1].



This metabolite is produced as a result of Aromatic *O-dealkylation,* a reaction predominantly involved in the activation of chemicals for eliciting ER binding activity

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[1]O. Mekenyan and R. Serafimova, *Mechanism based modeling of ER binding affinity: A COREPA implementation,* in *Endocrine Disruption Modeling*, J. Devillers, ed., CRC Press, France, 2009, pp. 259-294

[2]P. Paterson and J. Fry, Influence of cytochrome P-450 type on the pattern of conjugation of 4-hydroxybiphenyl generated from biphenyl or 4-methoxybiphenyl, Xenobiotica, 15(6) (1985), pp. 493-502.

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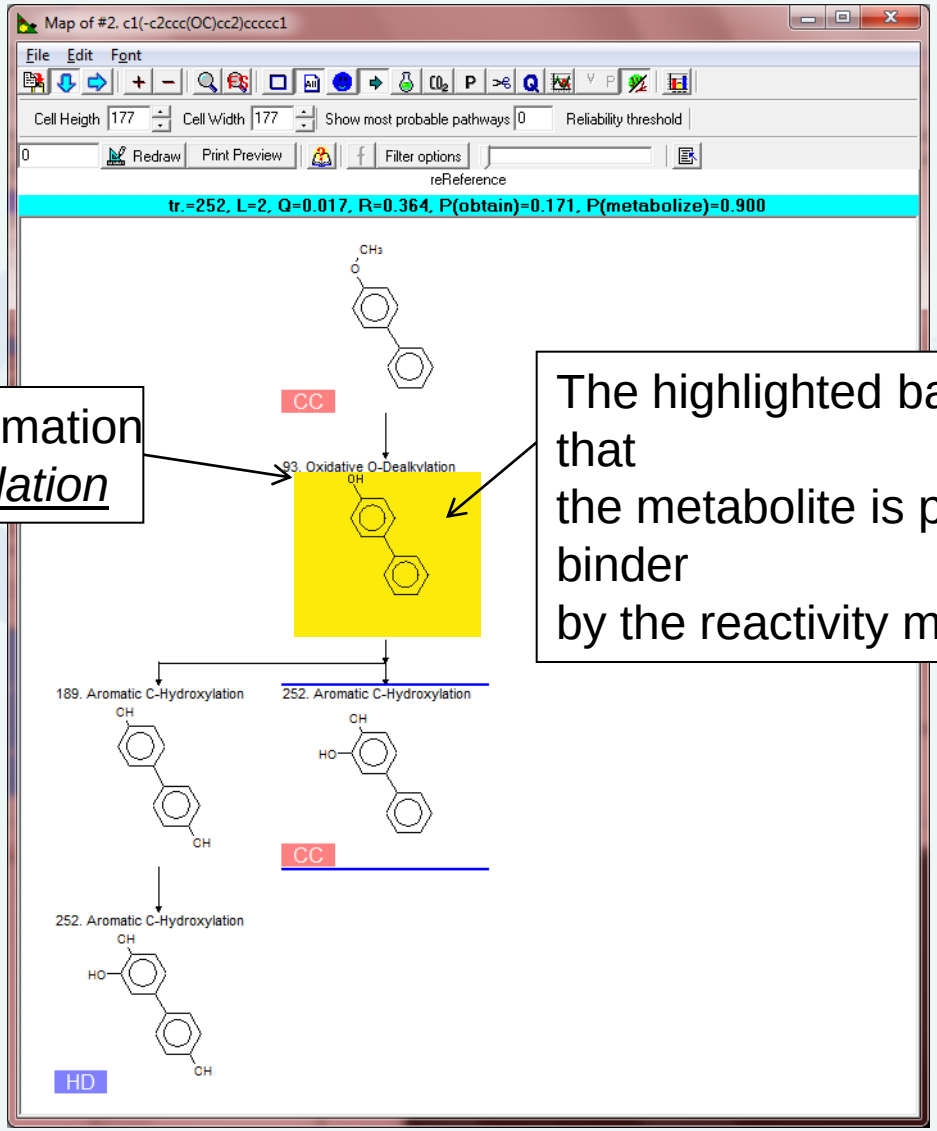
Simulated metabolic tree of Methoxybiphenyl in TIMES platform



Applied biotransformation
Aromatic O-dealkylation

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